Clinical Epidemiology and Global Health 9 (2021) 90–98

Contents lists available at ScienceDirect

Clinical Epidemiology and Global Health

journal homepage: www.elsevier.com/locate/cegh

Review article

Antivirals for COVID-19: A critical review

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ARTICLE INFO

Keywords:
Coronavirus
COVID-19
SARS-CoV-2
Antiviral

ABSTRACT

No specific drugs have been approved for coronavirus disease 2019 (COVID-19) to date as the development of antivirals usually requires time. Therefore, assessment and use of currently available antiviral drugs is critical for a timely response to the current pandemic. Here, we have reviewed anti-SARS-CoV-2 potencies of available antiviral drug groups such as fusion inhibitors, protease inhibitors, neuraminidase inhibitors, and M2 ion-channel protein blockers. Although clinical trials to assess the efficacy of these antivirals are ongoing, this review highlights important information including docking and modeling analyses, *in vitro* studies, as well as results from clinical uses of these antivirals against COVID-19 pandemic.

1. Introduction

The current coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a major threat to human civilization and leaves many challenges ahead.[1,2] As of July 11, 2020, there were more than 12 million confirmed cases of COVID-19, with more than 500,000 deaths.[3] The most common symptoms of COVID-19 include fever, dry cough, dyspnea, chest pain, fatigue and myalgia, whereas headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting are less commonly observed.[4] Although most of the SARS-CoV-2 infections are asymptomatic or have mild clinical symptoms, 20.3% of the hospitalized patients require intensive care unit (ICU) admission, resulting in a significant burden on healthcare facilities.[5] The disease severity, in part, seems to be associated with dysregulation of the host immune response.[6] The basic reproductive number (R_0) of SARS-CoV-2 is higher than that of SARS Coronavirus (SARS-CoV)[7] with a mortality rate of up to 6.2% as of April 13, 2020.[8]

SARS-CoV-2 belongs to the family *Coronaviridae*, subfamily *Coronavirinae* and genus *Betacoronavirus,* along with SARS-CoV and the Middle East respiratory syndrome coronavirus (MERS-CoV).[9,10] SARS-CoV-2 has a spherical enveloped particle-containing positive-stranded RNA that binds to the nucleocapsid (N) inside the membrane protein (M) and the envelope (E) comprises of glycoprotein spikes (S).[11] S protein is a primary receptor-binding domain (RBD) and is critical for viral entry into the host cells through cellular receptor angiotensin-converting enzyme 2 (ACE2).[12,13] Similar to other viruses, SARS-CoV-2 hijacks the host cell machinery and multiplies via viral attachment, fusion, penetration, uncoating, transcription, translation, and virion release.[14–18]

Specific effective drugs against SARS-CoV-2 have not yet been discovered and no specific drug has been approved for the treatment of COVID-19. Rapid assessment of the currently available antiviral drugs to be used for COVID-19 patients is therefore crucial in this time of crisis as well as discovering newer drugs.[5,19] Since the virus hijacks the host system via attaching to and then penetrating the host cells, followed by further critical steps (uncoating, reverse transcription, transcription, translation, and releasing of the virion), the principal target

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https://doi.org/10.1016/j.cegh.2020.07.006
Received 21 June 2020; Received in revised form 11 July 2020; Accepted 16 July 2020
Available online 28 July 2020

Abbreviations

$3CL^{Pro}$	3C-like cysteine protease
AAK1	AP2-associated protein kinase 1
ACE2	angiotensin-converting enzyme 2
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
E	envelope protein
ERGIC	endoplasmic reticulum-Golgi apparatus compartment
HA	hemagglutinin envelope glycoprotein
HAV	hepatitis A virus
HCV	hepatitis C virus
HE	hemagglutinin-esterase
HSV	herpes simplex virus
ICU	intensive care unit
INF-β	interferon
M	membrane protein
MERS-CoV	Middle East respiratory syndrome coronavirus
M^{pro}	main protease
N	nucleocapsid
NNRTI	non-nucleoside reverse-transcriptase inhibitors
NRTI	nucleoside reverse-transcriptase inhibitor
NRTTI	nucleoside reverse transcriptase translocation inhibitors
Nsp	non-structural protein
NtRTI	nucleotide reverse-transcriptase inhibitor
P^{pro}	papain-like protease
R_0	reproductive number
RdRp	RNA-dependent RNA polymerase
S	glycoprotein spike
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TMPRSS2	transmembrane serine protease 2

of antiviral drugs is to block the viral replication cycle at any of these stages. Currently, there are more than eighty antiviral drugs available and approved for treating viral infections in humans.[20] Over 50% of these drugs are used to treat HIV infection, with the rest being used against influenza A and B, Ebola virus, cytomegalovirus (CMV), hepatitis A and C virus (HAV and HCV), and herpes simplex virus (HSV). In the current pandemic, some available antivirals have been used to treat COVID-19 cases in some countries.[21,22] Since clinical trials to assess the efficacy of available antivirals for COVID-19 are still ongoing, the types of antivirals being used globally vary widely. This review summarizes antiviral drugs that can be potentially used for SARS-CoV-2 infection including the rationales, docking and modeling analysis, *in vivo* and *in vitro* findings, as well as results from new investigational drug protocols and clinical trials during this emergency and crisis.

2. SARS-CoV-2 life cycle and potential targets: The rationales

Major biochemical events and components in the replication cycle of coronavirus are considered as targets against which antiviral drugs are currently being developed. These include the spike protein,

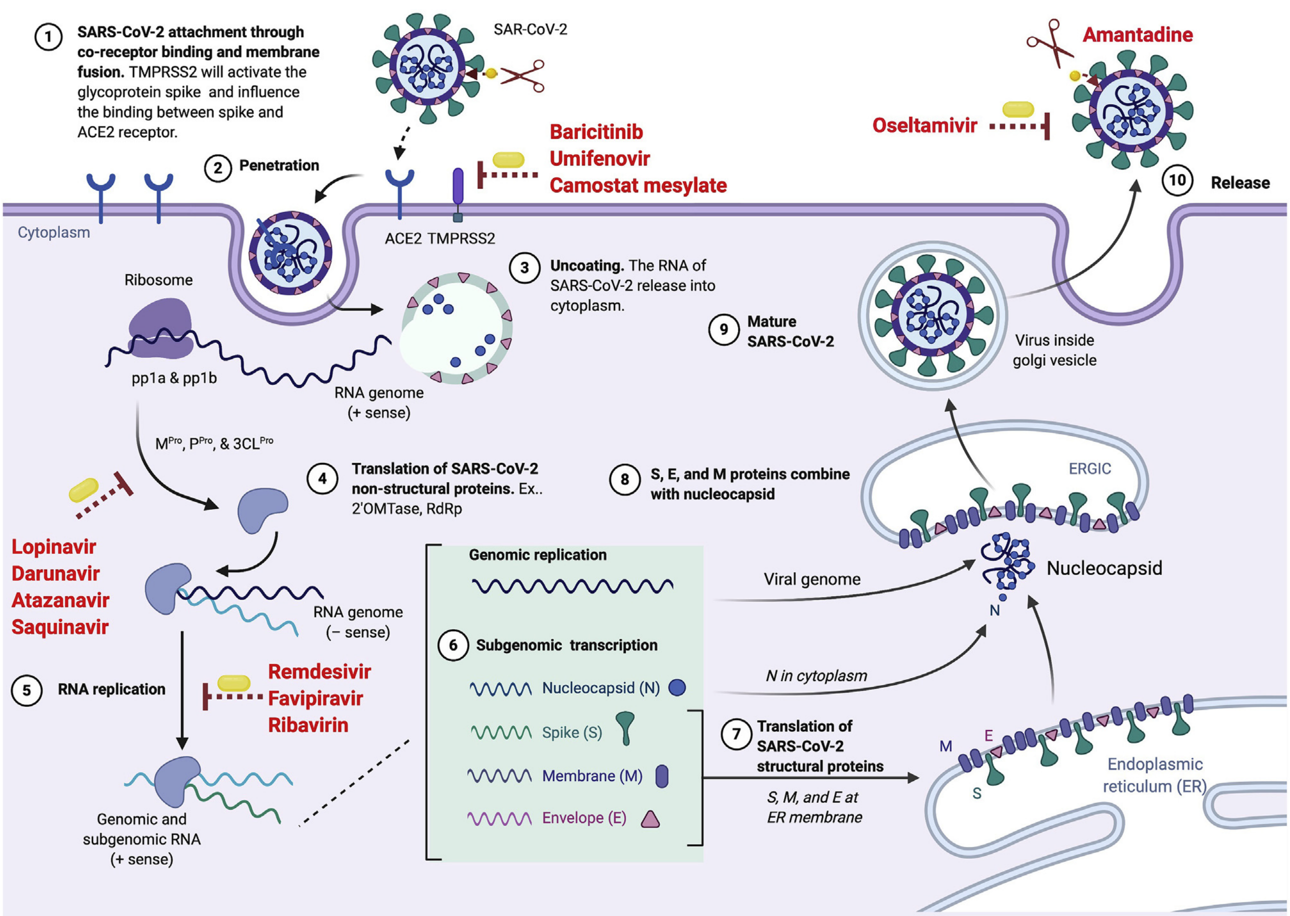

Fig. 1. The life cycle of SARS-CoV-2 and possible inhibition targets of antiviral drugs. Fusion inhibitors inhibit the fusion process of viral entry, while protease inhibitors target some proteases. Transcription inhibitors target reverse transcription step by blocking RNA-dependent RNA polymerase and therefore prevent viral replication. Some of the transcriptase inhibitors are nucleoside reverse-transcriptases. Some antivirals target M2 channel protein.

proteolytic enzymes, and RNA dependent RNA polymerase.[23] SARS-CoV-2 is transmitted among humans mainly via respiratory droplets, although it may also follow an airborne transmission mode.[24,25] The virus enters the host cells through two pathways, either via endosomes or plasma membrane fusion. In both mechanisms, the viral S protein mediates attachment to the membrane of the host cell and engages angiotensin-converting enzyme 2 (ACE2) as the entry receptor[26–29] (Fig. 1). A recent study showed the attachment between S protein and ACE2 is activated by a host protease called transmembrane serine protease 2 (TMPRSS2).[26,30] The virus uses S protein to neutralize antibodies, making it easier to bind to the host receptors.[31] Although the detailed fusion machinery of SARS-CoV-2 is not fully understood, *Betacoronavirus* mostly use hemagglutinin-esterase (HE) to link to sialic acid on the glycoprotein surface.[32,33] These fusion steps could be inhibited using fusion inhibitors (Fig. 2).

After the completion of fusion, the envelope is peeled off, and the genome of SARS-CoV-2, along with its nucleocapsid, penetrates the host cell cytoplasm (Fig. 1).[26,34,35] Its genome contains open reading frames 1a and 1b (*ORF1a* and *ORF1b*) genes that produce two polyproteins (pp), called pp1a and pp1b, that help in hijacking host ribosomes for viral translation process.[36,37] These polyproteins are then cleaved by main protease (M^{pro}) and papain-like protease (P^{pro}) to produce several non-structural proteins.[38] Beside M^{pro} and P^{pro}, 3C-like cysteine protease ($3CL^{Pro}$) has also been suggested to exist in SARS-CoV-2 based on 96% similarity with SARS-CoV using a three-dimensional analysis model.[39] Theses proteases are essential for viral replication and transcription[40] and protease inhibitors inhibiting these proteases (Fig. 2) are potential antivirals for SARS-CoV-2.

Subsequently, the replication process of the SARS-CoV-2 virus begins. Since the complete mechanisms of SARS-CoV-2 have not been thoroughly studied yet, the replication of SARS-CoV-2 can be explained based on SARS-CoV and MERS-CoV models. This is because the list of structural and non-structural proteins of SARS-CoV-2 is similar to those in these two viruses.[14] A non-structural protein, called nsp12 forms a replication and transcription complex called RNA-dependent RNA polymerase (RdRp).[41] In SARS-CoV, nsp12 associates with its cofactor (nsp7 and nsp8)[42,43] and this protein complex produces a complementary negative-sense RNA using the original positive RNA as a template. The negative-strand RNA is then used by viral replicase to synthesize new positive RNA molecules to process another translation and replication step to form the genome of the newest viral particles.[44] In SARS-CoV, topoisomerase III-beta mediates this process.[45] These stages may be disrupted using reverse transcription inhibitors.

Post-translational modification is required for assembly and budding of the enveloped virus. The sub-genomic RNA forms a structural protein complex including S, E, M and N.[46] S, E, and M then enter the endoplasmic reticulum.[46] The positive-strand RNA and N form a nucleoprotein complex in the cytoplasm.[47] Both complexes merge to complete the virus copy production in the endoplasmic reticulum-Golgi apparatus compartment (ERGIC). They are excreted to the extracellular region through the Golgi apparatus and vesicles as a mature virus and released from the cells to infect other cells.[48]

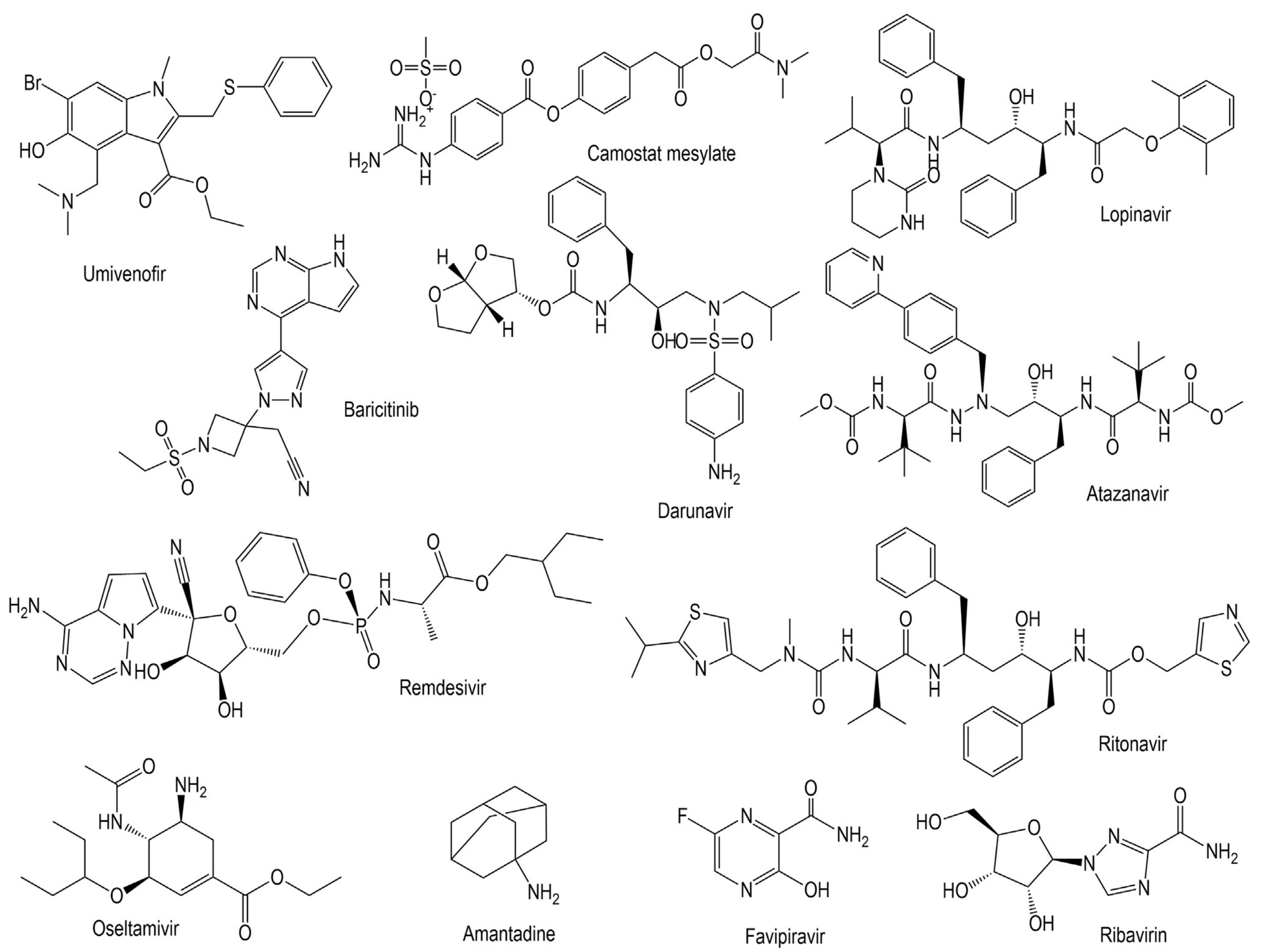

Fig. 2. Structures of selected antiviral drugs that have therapeutic potential against SARS-CoV-2. Baricitinib, umifenovir and camostat mesylate are fusion inhibitors while lopinavir darunavir and atazanavir are protease inhibitors. Reverse transcription inhibitors such as remdesivir, favipiravir (Avigan) and ribavirin, neuraminidase inhibitors such as oseltamivir and M2 ion-channel protein blockers (amantadine) are potential against SARS-CoV-2.

3. Antivirals for SARS-CoV-2 infection: results from labs, trials and patients

3.1. Fusion inhibitors

Fusion inhibitor is a group of antivirals that inhibit the fusion process during viral entry into the host cells (Fig. 1). Several drugs are available with umifenovir and camostat mesylate (Fig. 2) demonstrating antiviral activity against SARS-CoV-2.[49–52]

Baricitinib

Similar to other viruses, SARS-CoV-2 enters the host cells through receptor-mediated endocytosis. The process of endocytosis is regulated by AP2-associated protein kinase 1 (AAK1).[39] Therefore, the disruption of AAK1 will not only block the viral entry but also the intracellular viral assembly.[39] Baricitinib is a Janus kinase (JAK) inhibitor with high potential to bind to and inhibit AAK1.[53] Hence baricitinib can be used to inhibit both viral entry as well as the inflammatory response associated with SARS-CoV-2 infection (Fig. 2).[53] JAK inhibitors such as ruxolitinib and fedratinib that are closely related to baricitinib inhibited clathrin-mediated endocytosis at higher doses and hence these may not be effective in reducing the viral infectivity at tolerable doses.[54] Therapeutic use of baricitinib is associated with the occurrence of neutropenia, lymphocytopenia, and viral reactivation.[55] Since SARS-CoV-2 infected patients have a lower absolute lymphocyte count, use of baricitinib may increase the incidence of co-infection.[55] Further studies are required to analyze the risk-benefit ratio as well as the clinical utility of baricitinib therapy.

Umifenovir

Umifenovir, also called arbidol, is a nucleoside antiviral targeting the hemagglutinin envelope glycoprotein (HA) in the fusion machinery of influenza virus.[56] A recent study reported that umifenovir monotherapy to COVID-19 patients in China resulted in negative viral conversion where the virus was not detected in 14 days.[57] Randomized clinical trials are underway to assess the efficacy of umifenovir in China.[58,59] Arbidol and arbidol mesylate compounds have shown inhibitory effects on SARS virus-replication under *in vitro* conditions and are currently under trial to ascertain their therapeutic potentials in treating pneumonia caused due to SARS-CoV-2 in COVID-19 patients.[49,50]

Camostat mesylate

Camostat mesylate – a serine protease inhibitor – is another candidate drug that targets the fusion step in viruses. SARS-CoV-2 gains entry within the target host cells either through ACE-2 receptor and/or TMPRSS2 receptors, and camostat mesylate acts as a TMPRSS2 inhibitor.[60] It downregulates expression of SARS-CoV-2 spike (S) protein to prevent surface fusion and thereby blocks the cellular entry of the virus.[51,52] A previous study found that camostat mesylate prevented SARS-CoV entry into human bronchial epithelial cells.[61] Another *in vitro* study showed that camostat mesylate and E-64d (a cysteine protease inhibitor) could efficiently block TMPRSS2 binding of SARS-CoV-2.[26] Clinical trials are ongoing to assess the effectiveness of a combination therapy of hydroxychloroquine and camostat mesylate vis-a-vis hydroxychloroquine alone in Denmark[62] and Germany.[63]

Another serine protease inhibitor, nafamostat mesylate was found to possess 15-fold higher efficiency in inhibiting the entry of SARS-CoV-2 virus into host cells.[64] Hence due to its more potent antiviral activity and favorable safety profile, nafamostat mesylate can be considered as a better alternative to camostat mesylate.[64] Nafamostat mesylate is also used to treat disseminated intravascular coagulation (DIC). Hence, it will be further beneficial in managing the DIC with enhanced fibrinolysis seen in COVID-19 patients.[65]

3.2. Protease inhibitors

Some protease inhibitors such as lopinavir, darunavir, and atazanavir have the potential to be used against COVID-19[57, 66, 67] (Fig. 2). Computer-aided drug design techniques can be used for identifying potential drug repurposing candidates against viral proteases. In a computational drug repurposing study, drugs such as carfilzomib, valrubicin, eravacycline, lopinavir, and elbasvir were found to inhibit the main protease in SARS-CoV-2.[68] Further *in vitro* and *in vivo* studies are required to confirm the efficacy of these drugs.

Lopinavir

Currently, lopinavir is used in combination with ritonavir for treatment and prevention of HIV infection. It has been reported that lopinavir inhibited SARS-CoV-2 at a half-maximal effective concentration (EC_{50}) - the level of a drug that induces a response halfway between the baseline and maximum after a specified exposure time - of 26.36 μM.[69] Administration of lopinavir as an emergency drug in China increased the eosinophil count among COVID-19 patients.[70] In an *in silico* study, a combination of lopinavir and ritonavir – both used as HIV

Table 1
Current use of existing antiviral drugs for COVID-19.
Source: WHO,[68] China,[102] Japan,[72] Italy,[81] IPC,[73] Indonesia,[116] USA,[70] Singapore[71]

Class of drug	Current application	US FDA approved for current application	Emergency use for COVID-19
Fusion inhibitor			
Umifenovir (Arbidol)	Influenza	No	Singapore, China
Protease Inhibitor			
Lopinavir	HIV	Yes (September 2000)	USA, Japan, Singapore, Italy, China, IPC (Lopinavir-Ritonavir fix dose)
Darunavir	HIV-1	Yes (July 2016)	Italy (Darunavir-Ritonavir fix dose)
Atazanavir	HIV-1	Yes (July 2003)	Singapore
Saquinavir	HIV-1	Yes (December 1995)	Singapore
Nucleoside reverse transcriptase inhibitor			
Emtricitabine	HIV-1	Yes (July 2003)	Singapore (Emtricitabine-Tenofovir fix dose)
Azvudine	HIV-1	No	Singapore
Nucleotide reverse transcriptase inhibitor			
Remdesivir	Ebola	Not yet	WHO, IPC, USA, Singapore, Italy
Favipiravir (Avigan)	Influenza	Not yet	Singapore, Japan, Indonesia
Ribavirin	HCV	Yes (April 2004)	Singapore, IPC
Sofosbuvir	HCV	Yes (December 2013)	Singapore
Neuraminidase inhibitor (Virus release inhibitor)			
Oseltamivir (Tamiflu)	Influenza A & B	Yes (December 1999)	IPC, Singapore, Indonesia

IIPS, International Pulmonologist's Consensus including USA, India, Iran, China, Italy, Great Britain, EUA, Colombia, Egypt, Singapore, Romania, Ireland, Malaysia, Saudi Arabia, Sudan, Greece, and Bolivia.

protease inhibitors – inhibited the main protease (M^{Pro}) of SARS-CoV-2 [71]. A previous study showed that a specific combination of lopinavir-ritonavir, known as Kaletra® demonstrated antiviral effects against SARS-CoV both *in vitro* and in clinical trials.[72] Therefore, the lopinavir-ritonavir combination is being used as an emergency treatment for COVID-19 patients in some countries[73,74] (Table 1). Lopinavir-ritonavir alone or in combination with interferon (INF)-β – an inflammation regulator molecule – have been listed by WHO as options for "solidarity" clinical trial for COVID-19.[75] Ritonavir-lopinavir commination could reduce the viral load and improve the clinical symptoms of COVID-19.[57] Combination of ritonavir-lopinavir and umifenovir also substantially halted the progression of lung damage too.[76] In one study, lopinavir-ritonavir treatment was associated with a better outcome but did not significantly accelerate the clinical improvement of severe COVID-19 infection.[74] Although the efficacy of lopinavir has not been assessed for COVID-19, ritonavir-lopinavir combination has been used in treating COVID-19 cases in some countries such as the USA,[77] Singapore,[78] Japan[79] and other countries that follow International Pulmonologists consensus[80] as emergency response measures (Table 1). Clinical trials are ongoing to assess the efficacy of lopinavir-ritonavir for COVID-19 in China,[81] Canada,[82] Spain,[83] France,[84] Hong Kong,[85] Thailand,[86] and the US.[87]

Darunavir

Darunavir, an anti-HIV drug, has been recommended for COVID-19 treatment in Italy.[88] It is used in a combined regimen along with cytochrome P-450 inhibitors like ritonavir or cobicistat and *in vitro* studies have demonstrated their replication inhibitory effect against SARS-CoV-2.[66] A clinical trial in Thailand is underway to assess the effectiveness of darunavir combination with other antivirals and hydroxychloroquine for COVID-19 patients.[86] A combination of darunavir and cobicistat is also being tested in an ongoing clinical trial in China.[89] A fixed-dose combination of darunavir and cobicistat, known as PREZCOBIX®, is also being used to treat COVID-19 (Table 1).[90] Recently, HIV positive patients who were already under treatment with darunavir, were found to be infected with COVID-19, raising concerns over the efficacy of this HIV protease inhibitor.[91] This suggests that darunavir might not be effective in preventing SARS-CoV-2 infection at the current adopted dosage of 800 mg.[91]

Atazanavir

An *in silico* study showed that atazanavir bound more strongly to the active site of SARS-CoV-2 M^{Pro} as compared to lopinavir[67] and an *in vitro* study found that atazanavir inhibited SARS-CoV-2 replication.[67] A previous study on HIV infected patients showed that a combination of atazanavir with ritonavir improved glucose uptake and lipid parameters and decreased fasting glucose more effectively as compared to lopinavir-ritonavir combination.[92,93] This suggests that atazanavir might be an alternative for lopinavir when combined with ritonavir for COVID-19 treatment; however, further study is warranted. Currently, this antiviral drug is as an option for COVID-19 treatment (Table 1).

Saquinavir and other protease inhibitors

Saquinavir and other protease inhibitors such as indinavir, amprenavir, and nelfinavir might also display similar effects against COVID-19 like protease inhibitors mentioned earlier, due to a high degree of similarity between the structures (Fig. 1). An *in silico* study demonstrated that saquinavir and indinavir inhibited $3CL^{Pro}$ activity in SARS-CoV-2.[94] Another study showed that saquinavir, indinavir, amprenavir and nelfinavir inhibit SARS-CoV-2 *in vitro*[95] with nelfinavir showing the best inhibition in comparison with others.[95] Saquinavir has been used in treatment of COVID-19 patients in Singapore (Table 1). In another computational study, two more candidates were identified, raltegravir and paritaprevir that showed the potential to inhibit $3CL^{Pro}$ activity in SARS-CoV-2.[96] Recently, potential anti-viral phytochemicals that have activity against the $3CL^{pro}$ of SARS-CoV-2 were identified while screening medicinal plant library and the top antiviral candidates identified can be further evaluated using *in vitro* studies.[97]

3.3. Reverse transcription inhibitors

Another strategy to combat SARS-CoV-2 infection involves targeting the reverse transcription step by blocking RdRp and therefore preventing viral replication (Fig. 1). A few potential inhibitors are nucleoside reverse-transcriptase inhibitors (NRTIs), nucleotide reverse-transcriptase inhibitors (NtRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs) and nucleoside reverse transcriptase translocation inhibitors (NRTTIs).

Remdesivir

Remdesivir is a monophosphoramidate prodrug with a molecular mass of 602.6 g/mol and chemical formula $C_{27}H_{35}N_6O_8P$. Designated as GS-5734, remdesivir is a nucleotide analog possessing a wide spectrum of antiviral properties against majority of the single stranded RNA viruses like coronaviruses (including MERS-CoV and SARS-CoV-2) Lassa fever virus, Junin virus, Ebola-Marburg virus, respiratory syncytial virus, Nipah virus and Hendra virus.[98,99] After entering the host cells, GS-5734 is metabolized into GS-441524 that is capable of reducing RNA replication of SARS-CoV, MERS-CoV, zoonotic and endemic human delta coronaviruses under *in vitro* conditions, while *in vivo* results have shown antiviral potential against bat and human coronaviruses in primary epithelial and lung cell culture systems.[100,101]

Remdesivir is an NtRTI drug that is worthy of a "solidarity" clinical trial for COVID-19, according to WHO.[75] It acts as an RNA-dependent RNA polymerase (RdRp) inhibitor[100] and its pharmacokinetics and characteristics have been studied in SARS-CoV and MERS-CoV infections.[102] It alters functions of viral exonuclease and due to disturbed proof reading, viral genomic RNA replication and production declines.[98] Since it can prevent viral replication and can be recommended for COVID-19 patients to prevent the severity of disease progression, randomized, double blind clinical trials with such patients are underway in phase-3 to confirm the therapeutic potential of remdesivir.[66,103]

Previous studies found that remdesivir was effective against MERS-CoV; it reduced the viral loads in the affected part in mice, therefore supported to regain the normal pulmonary functions[104,105] and was also proposed as a therapeutic agent against SARS-CoV-2.[106] A preliminary study found that the viral load in nasopharyngeal and oropharyngeal swabs reduced significantly after 12 days of remdesivir administration.[107] An *in vitro* study reported that a combination of remdesivir and chloroquine, an anti-malarial drug, effectively inhibited SARS-CoV-2 growth in Vero E6 cells.[108] Clinical trials are ongoing to assess the efficacy of remdesivir for COVID-19 in the US,[109] Norway,[110] and France.[111] Remdesivir has been used to treat COVID-19 cases in the USA and Singapore. The first case of COVID-19 in the USA was recovered using intravenously administered remdesivir[107] (Table 1).

Favipiravir (Avigan)

Favipiravir (T705), a purine (guanine) nucleotide analog is a derivative of pyrazine carboxamide (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) and an RdRp inhibitor.[112] It was initially developed against influenza but attracted attention for COVID-19 treatment due to its large spectrum antiviral properties.[113] Favipiravir is a prodrug and becomes an active molecule called favipiravir ibufuranosyl-5′-triphosphate (T-705-RTP) upon administration.[114] It competes with guanine nucleosides during RNA viral replication by getting integrated with viral RNA, resulting in selectively blocking the RdRp to arrest the synthesis of viral RNA.[115] Favipiravir is considered as a potential candidate drug for COVID-19, however while administering favipiravir, drug-drug interaction must be taken into consideration with already prescribed medication which may alter the pharmacokinetics and plasma concentration of favipiravir.[116,117] This antiviral was associated with rapid clearance of Ebola virus in an animal model.[118] Ongoing clinical trials in China[119] report favipiravir treatment in patients was significantly correlated with a shorter viral clearance time as compared to untreated patients.[120] Its efficacy has also been assessed in a randomized clinical trial.[121] Favipiravir is currently being used for COVID-19 treatment in Japan[79] and Indonesia[122] (Table 1).

Ribavirin

Ribavirin is a guanine derivative analog that has antiviral activity against HCV, with an *in vitro* study report that it has antiviral activity against SARS-CoV-2.[123] FDA advocated the therapeutic efficiency of ribavirin, remdesivir, penciclovir, favipiravir, nitazoxanide, nafamostat, and chloroquine against this strain based on *in vitro* trials.[124]

Ribavirin antiviral mechanism works to hamper the function of polymerases, hinders the RNA capping to destabilize the viral RNA and finally obstruct replication. Along with this, ribavirin inhibits the function of inosine monophosphate dehydrogenase enzyme to prevent the production of guanosine and hence promotes degradation of viral RNA.[125] If at all any replication would with ribavirin intake, probability of arbitrary mutation in the RNA is immense, leading to loss of virulence in progeny viruses.[124]

Its efficacy in treating SARS-CoV-2 patients is being tested in clinical trials in Hong Kong.[126] According to the Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced pneumonia in China for temporary treatment of COVID-19, ribavirin is one of recommended drugs that is administered with a combination with either IFN alpha or lopinavir-ritonavir.[127] Docking and modeling analysis using ribavirin together with sofosbuvir and remdesivir indicated that ribavirin is a promising candidate drug for COVID-19 treatment and can be administered either by intra-venous route or orally.[128] Ribavirin and sofosbuvir are currently part of the therapeutic regimen to treat COVID-19 in some countries (Table 1).

Other transcription inhibitors

Other FDA approved NtRTIs such as adefovir, tenofovir alafenamide, tenofovir disoproxil, abacavir, ganciclovir, and didanosine have similar structural characteristics either with remdesivir or ribavirin, and therefore, probably have antiviral activity against SARS-CoV-2. Other transcriptase inhibitor drugs such as NRTIs (lamivudine, stavudine, zidovudine, emtricitabine, zalcitabine, and azvudine) and NNRTIs (efavirenz, nevirapine, delavirdine, and rilpivirine) might also have antiviral properties against SARS-CoV-2. Though some of them have been evaluated *in silico* through molecular docking studies,[129] further studies are warranted to ascertain their clinical efficiency.

3.4. Neuraminidase inhibitors

Oseltamivir – a neuraminidase inhibitor – is effective in preventing influenza[130] and was successful in treating influenza in children.[131] Neuraminidase inhibitor drugs such as oseltamivir, zanamivir, and peramivir, are not expected to be effective against COVID-19, mainly because neuraminidase has not been found in SARS-CoV-2. However, studies have reported the use of a combination of oseltamivir with ganciclovir and lopinavir/ritonavir to treat COVID-19 patients in Wuhan.[132,133] A computational study also supported synergistic effects of oseltamivir-lopinavir-ritonavir combination against SARS-CoV-2.[134] Oseltamivir administered with ceftriaxone and terbutaline has been used to treat COVID-19 cases in Afghanistan.[135] A case report also found that the CT-scan of the lungs of a COVID-19 patient showed significant improvement after a three day course of oseltamivir.[136] Oseltamivir is currently being used as a recommended option for COVID-19 treatment in Indonesia and Singapore (Table 1).

3.5. M2 ion-channel protein blockers

The M2 channel protein on the viral envelope is essential in maintaining pH across the viral envelope that is critical during cell entry and movement across the trans-Golgi membrane of host cells during viral maturation. This M2 ion-channel protein is one of the targets to combat influenza viruses.[137] The structures of some M2 ion-channel protein inhibitors such as amantadine, adamantane, and rimantadine are represented in Fig. 2. A previous study showed that amantadine could block the p7 protein of HCV that is crucial in forming ion channels in host cell membranes.[138] A report in 1973 showed that amantadine had a potent effect against Coronavirus 229E *in vitro*,[139] and later a report also showed that amantadine was able to block protein-membrane channel activity of SARS-CoV.[140] Despite increasing evidence suggesting that amantadine has antiviral potency suitable for COVID-19 therapy,[141,142] more studies are warranted to assess its efficacy.

4. Non-antiviral drugs against SARS-CoV-2 infection: Old dog new tricks

4.1. Importin α/β1-mediated nuclear import inhibitors

An FDA-approved broad-spectrum antiparasitic drug called ivermectin has recently exhibited potent *in vitro* antiviral activity against SARS-CoV-2. A single dose of the drug induced ~5000-fold reduction in viral RNA content.[143] The broad-spectrum antiviral activity of ivermectin against several RNA viruses is mediated by the inhibition of importin α/β1-mediated nuclear import.[143] SARS-CoV-2 being an RNA virus, a similar mechanism is expected to facilitate the inhibitory activity of ivermectin.[143] The drug combination of ivermectin and hydroxychloroquine was proposed as a combination therapy for the prophylaxis or treatment of COVID-19. This combination may produce a synergistic effect due to the inhibition of both, viral entry as well as viral replication.[144] However pharmacokinetic analysis indicates that higher dosage is required for achieving the antiviral activity. Therefore, the recommended inhibitory concentration is very difficult to administer in human beings.[145] In a recent observational case-controlled study, ivermectin therapy at a dose of 150 mcg/Kg was reported to lower the mortality rate as well as the duration of hospital stay.[146] Further randomized clinical controlled studies are required before concluding the efficacy of ivermectin in SARS-CoV-2 infected patients.

4.2. Chloroquine and hydroxychloroquine: repurposed drug, FDA approved

Chloroquine (9-aminoquinoline) is a proven and reliable anti-malarial drug, which has been found useful against SARS-CoV-2 infections and hence is now proposed and approved to be used for the treatment of COVID-19 patients by clinicians, with its new insights being explored fully.[33,147,148] It blocks the entry of the virus by either altering the structural configuration of cell receptors or by competitively binding to the cellular receptors.[149] It can amend the glycosylation of ACE-2 cellular receptors needed for SARS-CoV-2 entry.[149] On the other hand, this drug can also reduce synthesis of sialic acid receptors to prevent the attachment of SARS-CoV-2 to the host cells. Chloroquine and hydroxychloroquine possess better binding affinity to host cell receptors as compared to the S protein of SARS-CoV-2 and therefore due to competitive binding to sialic acid and gangliosides present on the surface of the target cell, it prevents attachment and entry of the virus.[150] In addition to the antiviral activity, chloroquine possesses anti-inflammatory activity that might contribute to its efficacy in treating COVID-19 patients. Studies conducted on animal models of melioidosis suggest that the anti-inflammatory property of chloroquine is mediated by the inhibition of glycogen synthase kinase-3β.[151] Before the large-scale recommendation of off-label use, the potential of chloroquine to cause detrimental cardiac effects must be considered.[152] Currently a randomized controlled trial has been registered to evaluate the prophylactic potential of hydroxychloroquine in preventing secondary infections and severe clinical symptoms among individuals who came into contact with SARS-CoV-2 infected individuals.[153]

5. Conclusion and further perspectives

Even though specific antiviral drugs for COVID-19 have not been discovered or approved by the FDA, the use of some available antiviral drugs that target specific steps within the life cycle of SARS-CoV-2 could be an alternative therapeutic strategy for dealing with this pandemic. Fusion inhibitors, protease inhibitors and transcription inhibitors are some of the promising groups of antivirals to be considered for the same. Apart from antiviral drugs, several promising approaches are also being used to treat COVID-19 such as convalescent plasma, the use of which has shown a reduction in viral load and morbidity of patients.[154,155] IFN-α/β[156,157] and IL-6R inhibitor[158,159] have also showed promising effects and are currently being assessed in several clinical trials.

Funding

This compilation is a review article written by its authors and required no substantial funding to be stated.

Declaration of competing interest

All authors declare that there exist no commercial or financial relationships that could, in any way, lead to a potential conflict of interest.

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